

believe that priority assessment in patients awaiting heart transplantation on the basis of QT dispersion measurements is premature.

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Reply

We appreciate the interest of Zabel and colleagues in our recent report (1). We also agree that it is important to be clear regarding the interpretation of our results. We would like to respond to their comments.

1. The analysis of QT dispersion risk used two different measures of dispersion: the maximal – minimal QT interval (QTDISP) and the coefficient of variation of all QT intervals (QTCV). These variables were highly significant ($p = 0.009$ and $p = 0.001$, respectively) when analyzed as continuous variables without selection of a cutoff. The dichotomization of patients on the basis of a cutoff for QTDISP of 140 ms and QTCV of 9% presented in our report was for illustrative purposes only. The actual statistical model yields a continuum of risk based on the value for QTDISP and QTCV. The significance of these predictors remained after adjustment for other potential risk factors in a multivariate analysis and after the removal of the 13 subjects with atrial fibrillation. It can be seen in the original report that all analyses consistently showed the utility of QT dispersion as a risk factor when measured as described in the patient cohort under study (1).

Recent prospective studies (1,2) have demonstrated a significant correlation between QT dispersion and mortality in patients with heart failure, although some preliminary studies may suggest otherwise. It is reasonable to assume that patients awaiting heart transplantation represent a sicker subset of patients whose data may not be extrapolated to patients with heart failure in general. We look forward to reading the final published reports on the subject alluded to by Zabel and colleagues (3,4).

2. The issue is raised that U waves may have contributed to an increase in measured QT dispersion in the patients studied. However, U waves were not included in the analysis (1) and therefore did not contribute to increased QT dispersion in the original report.

3. In terms of electrocardiographic (ECG) analysis, the ECGs were read by two independent observers blinded as to outcome, with the aid of a magnifying lens, without a digitizing pad. The method for obtaining ECGs was, as surmised, a standard 4×3 format. We used this ECG format because it is currently the standard method for obtaining ECGs and therefore most widely applicable with existing equipment. Although transient changes in heart rate during the brief period of acquisition could have affected QT dispersion, we doubt that a sizable and systematic pattern would have occurred that would have affected its measurement.

4. We considered the possibility that patients with atrial fibrillation whose RR intervals can vary from beat to beat could have affected the interpretation of our data. In fact, not only did we consider this possibility, but we included specific data on this subject in the published report (1). Although patients with atrial fibrillation were included in most of the overall analyses, we did report specific data in which the 13 patients with atrial fibrillation were excluded from analysis (see Fig. 3 and the results and discussion sections). Indexes of QT dispersion remained significant predictors of risk both before and after the 13 subjects with atrial fibrillation were removed from the analysis.

As ardent students of the scientific process, we hope that our work serves as the springboard for additional studies in this area, so that we can ultimately know how to best select patients who are still likely to die while awaiting a donor heart.

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Echocardiography in *Staphylococcus aureus* Bacteremia

Fowler et al. (1) investigated the diagnostic and prognostic usefulness of transesophageal echocardiography (TEE) in patients with *Staphylococcus aureus* bacteremia. The authors suggest that infective endocarditis is common in patients with *S. aureus* bacteremia and is

associated with an increased risk of death from sepsis. They further conclude that TEE is frequently needed to make the diagnosis of infective endocarditis and should be considered in all patients with *S. aureus* bacteremia. We agree that bacteremia is a serious condition and is associated with morbidity and mortality, and we commend the authors on their efforts to identify patients with infective endocarditis among this group. However, we believe that their conclusions are not justified on the basis of their study.

1. It is unclear exactly what hypothesis the authors were trying to test and how they designed the study to test it. They appear to want to evaluate the use of TEE in the diagnosis of infective endocarditis and to demonstrate that it is better than transthoracic echocardiography (TTE) for this purpose. This approach is problematic because the authors used TEE as part of the reference standard (along with the Duke criteria) for the diagnosis of infective endocarditis. They had no way of addressing specificity, and the sensitivity of TEE is naturally better than TTE because they considered TEE the reference standard. Thus, their study is not appropriately designed to determine whether TEE is better than TTE in this setting.

2. The authors evaluated only 59% of eligible patients with *S. aureus* bacteremia. The remaining patients were not evaluated because of either patient or physician refusal. Thus, their sample may not be representative of the intended study population. Furthermore, although the authors present the demographic and clinical characteristics of both the study and excluded groups, they did not report any statistical comparisons. When we made calculations based on the present data, there appeared to be significant differences between included and excluded patients. The proportion of patients with an unknown source of bacteremia in each group is significantly different ($p = 0.001$), as is the proportion of patients with catheter-related sepsis ($p = 0.001$). These baseline differences are significant even after adjustment for multiple comparisons and strengthens the premise that their sample may not be representative of all patients with *S. aureus* bacteremia. Specifically, the excluded group had a higher percentage of unknown infection source and a lower percentage of a catheter source. How these exclusions affect the authors' conclusion is unclear; however, the direction of any bias inherent in the selection of cases should be addressed.

3. The authors analyzed multiple outcomes between subjects with and without infective endocarditis. They claim that death due to *Staphylococcus* sepsis was significantly more likely in patients with infective endocarditis. The p value by Fisher exact test for this comparison is 0.034. Not only is this misreported twice as 0.003 in the report, but no mention of multiple comparisons is made. With four outcome measures being compared, the risk of a type I error is 0.20 (if α is 0.05). Using the Bonferroni correction, the α value for a significant difference should have been set at 0.0125. Thus, statistical significance was not achieved. Hence, there may not be a difference between the groups with and without infective endocarditis as far as death due to *S. aureus* bacteremia.

4. No information was provided concerning the specific treatment regimens administered during the prospective evaluation. Differences in treatment regimen in either group would either enhance or dilute any outcome relation.

In conclusion, the unclear hypothesis, sampling procedure, differences between included and excluded patients, statistically weak conclusions and lack of standardized treatment protocols make it difficult to accept the generalizability of their conclusions. We feel that this study does not establish routine TEE in patients with *S.*

aureus bacteremia as the basis for future evaluation of clinical therapies.

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Reply

We thank Guzzo and Simpson for their interest in our report and for the questions that they raise regarding various aspects of it. We would like to clarify several points that address these misunderstandings.

Our colleagues suggested that we were using transesophageal echocardiographic (TEE) findings as our reference standard for the diagnosis of endocarditis. This suggestion is incorrect. We used the Duke criteria as the reference standard measure by which the diagnosis of endocarditis was made (see Table 2). This diagnostic schema is both sensitive (1-4) and specific (1,5) for the diagnosis of endocarditis and has been validated at Duke and elsewhere. TEE findings merely fulfilled a portion of these diagnostic criteria, which also include clinical and microbiologic criteria. Thus, the diagnosis of endocarditis in our report rested upon a validated diagnostic schema.

Guzzo and Simpson suggested that the group of patients undergoing TEE might not be representative of the intended study population because excluded patients who were significantly more likely to have no identifiable focus of infection and were significantly less likely to have an intravascular catheter source of infection. Indeed, these facts would make excluded patients more likely to have endocarditis, thus supporting our findings. The absence of an identifiable focus of infection among patients with *Staphylococcus aureus* bacteremia is a powerful risk factor for endocarditis (6), and patients with an intravascular device are at low risk for endocarditis when the catheter is promptly removed (7-9). Thus, the effect of the excluded patients would be underestimation of our findings. In other words, had fewer patients with a nonidentifiable focus of infection been excluded, an even higher rate of endocarditis might have occurred.

Our colleagues took issue with the statistical evidence surrounding the mortality of patients with and without endocarditis. We acknowledge that the correct p value for patients dying of *S. aureus* endocarditis is 0.03, as we reported in the abstract section. Furthermore, as demonstrated by the fact that our colleagues performed the calculation, we have provided the discerning reader with the means of calculating Bonferroni corrections should it be considered necessary. However, we interpret our finding as significant, because it makes numerical (15.4% mortality rate among endocarditis patients versus 2.6% among patients without endocarditis) and clinical sense (patients with endocarditis are more likely to die than patients without endocarditis), as well as being statistically valid.

Finally, Guzzo and Simpson suggested that differences in treatment regimen would have an impact on patient outcome. Although we agree